CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
METHOPRENE

Chemical Code # 001784, Tolerance # 00359
SB 950 # 173
February 5, 2003

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, inadequate study, no adverse effect indicated
Subchronic, rat:	Inadequate study
Chronic toxicity, dog:	Data gap, no study submitted.
Subchronic, dog:	Inadequate study
Oncogenicity, rat:	Data gap, inadequate study, no adverse effect indicated
Oncogenicity, mouse:	Data gap, inadequate study, no adverse effect indicated
Reproduction, rat:	Data gap, inadequate study, no adverse effect indicated
Teratology, rat:	Data gap, invalid IBT study
Teratology, rabbit:	Data gap, inadequate study, no adverse effect indicated
Teratology, Mice	Data gap, inadequate study, no adverse effect indicated
Gene mutation:	No data gap, no adverse effect indicated.
Chromosome effects:	Data gap, inadequate study, no adverse effect indicated
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.
All record numbers through 038071 and 900000+ were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T030205
Original: Kishiyama and Gee, February 5, 2003

Methoprene, an insect growth regulator, has been classified as a biochemical by the US EPA. See the Reregistration Eligibility Decision document of 1991 and the updated Fact Sheet of June, 2001. Because the data base available was more complete than currently required for biochemicals at the time of the 1991 RED, the US EPA determined that no further health effects studies were required. Although the data base consists of studies conducted primarily in the 1970's, therefore not complying with current guidelines, there is no evidence of significant concerns regarding potential human health effects. (Gee, 2/5/03)

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC TOXICITY, RAT

Subchronic, rat:

030 977526 Jorgenson, T. A. and D. P. Sasmore "Toxicity studies of Altosid™ technical (1) ninety-day subacute in rats (2) ninety-day subacute in dogs." (SRI, LSC-1833, November, 1972) Altosid™ technical, batch S-1026Z-I (68.9%T) was fed in the diet to 15 Sprague-Dawley rats/sex/dose at 0, 250, 500, 1000 and 5000 ppm for 90 days. Dose selection was based on a 2-week range-finding study. Hematology analysis was done on 5/sex/group at weeks 4, 8 and 13. Serum chemistry and urinalysis were performed at termination. Tissues from 10/sex in the control and 5000 ppm groups were examined microscopically. There were no effects on clinical signs, body weight, food consumption, hematological parameters or clinical chemistry. Liver weights were increased at 5000 ppm for both sexes and kidney weight of male rats were increased. Histopathology showed renal tubular regeneration in males (7 or 10, unclear) at 5000 ppm and 3 males at 1000 ppm. Otherwise, there appeared to be no other findings in the limited report. Nominal NOEL probably 500 ppm based on kidney findings in males. UNACCEPTABLE (insufficient information). No worksheet. (Gee, 2/4/03)
EPA: The RED of 1991 gave a NOEL for systemic toxicity of 500 ppm based on degeneration in the kidney, apparently an error as the report itself states it was regeneration.

Chronic, rat:

109 038067 Same study as 002 977535.

002 977535 Wazeter, F. X and Goldenthal, E. I. "Two Year Oral Toxicity Study in Rats (Altosid)." (International Research & Development Corporation, Report Number 322-001, October 14, 1975.) Methoprene , purity 86.9%, was admixed with the feed at concentrations of 0, 250, 1000, or 5000 ppm and fed to 50 Sprague-Dawley rats/sex/group during 104 weeks. Hematology, clinical chemistry and urinalysis on only 5/sex/group. Ophthalmology was performed on all rats at 3, 6, 12, 18 and 24 months. No evidence of toxicity reported. Nominal NOEL = 5000 ppm. UNACCEPTABLE (major variances and insufficient information including no analysis of diets, no justification of dose selection, inadequate histopathology - see worksheet). Not upgradeable. (C. M. Oshita and J. Christopher, 5/22/85).

CHRONIC TOXICITY, DOG

No study submitted

Subchronic, dog:

030 977526 Jorgenson, T. A. and D. P. Sasmore "Toxicity studies of Altosid™ technical (1) ninety-day subacute in rats (2) ninety-day subacute in dogs." (SRI, LSC-1833, November, 1972) Altosid™ technical, batch S-1026Z-I (68.9%T) was fed in the diet to groups of 4 beagle dogs/sex/dose at 0, 250, 500 and 5000 ppm for 90 days. Dose selection was based on a 2-week range-finding study. Hematology/clinical chemistry and urinalysis were performed pretest, and at 4, 8 and 13 weeks. Most parameters were measured. Ophthalmologic exams were done pretest and at termination for all dogs. Tissues from the controls and high dose groups were examined

histologically. Body weight and food consumption in all groups were normal as were hematology parameters and eye exams. Alkaline phosphatase levels were significantly higher at 5000 ppm in male dogs at all sampling times and in females at 8 weeks. Relative liver weights were also increased at the high dose. No treatment-related histopathological findings were reported. Nominal systemic NOEL = 500 ppm. UNACCEPTABLE (insufficient information) No worksheet. (Gee, 2/4/03)
EPA: In the 1991 RED for methoprene, US EPA indicated the NOEL as 500 ppm based on the elevated alkaline phosphatase and increased liver weights.

027 977530 Sasmore, D. P. Supplementary histopathology report for 977526, dated October 8, 1973. US EPA requested that tissues from the low and intermediate groups be examined for histological effects. The lesions that were found were considered to be incidental by the pathologist. No change in status. No worksheet. (Gee, 2/4/03).

ONCOGENICITY, RAT

109 038067 Same study as 002 977535.

ONCOGENICITY, MOUSE

002 977540 Wazeter, F. X. and Goldenthal, E. I. "Eighteen Month Carcinogenic Study in Mice." (International Research & Development Corporation, March 14, 1975.) Methoprene , purity 87%-88%, was admixed with the feed at concentrations of 0, 250, 1000, or 2500 ppm and fed to 50 CD-1 mice/sex/group for 72-78 weeks. No evidence of toxicity reported. Nominal NOEL = 2500 ppm. UNACCEPTABLE (insufficient information including no justification of doses, no analysis of diets for content of test article, limited histopathology on interim deaths, methods inadequately described, others - see worksheet) . (C. M. Oshita and J. Christopher, 5/23/85).
US EPA determined that the systemic NOEL for this study was 250 ppm, based on unidentified brown pigmentation of hepatocyte cytoplasm of males (18/30) and females (9/24) at termination at 2500 ppm and of 2/10 females (all that were examined) at 1000 ppm with 0/10 for males. There were 0/32 males and 0/24 females in the control groups. No data were included for interim deaths. In the 1991 RED, the 250 ppm (37.5 mg/kg/day) was used to establish the chronic oral reference dose of 0.4 mg/kg/day (page 11).

REPRODUCTION, RAT

013 977550 Killeen, Jr., J. C. and W. R. Rapp. "A Three Generation Reproduction Study of Altosid® in Rats." (Bio/Dynamics Inc., Report Number 73R-892, November 8, 1974.) Methoprene (Altosid), purity 86.9% to 87.5%, was admixed with the feed at concentrations of 0, 500 and 2500 ppm and fed continuously through 3 generations, 1 litter per generation, to 20 Long-Evans rats/sex/group. There were fewer than 20 pregnant females per group per generation. There was no histopathology conducted on adult breeders. There were no affects reported at the high dose, therefore the nominal NOEL = 2500 ppm. UNACCEPTABLE (major variances and insufficient information). Not upgradeable (only two doses with the high dose inadequate, lack of histopathology, too few pregnant females per generation, no diet analysis, others - see worksheet) (C. M. Oshita and J. P. Christopher, 5/23/85).

110 038068: same study as 977550.

TERATOLOGY, RAT

030 024195 "Teratology Study with Altosid Technical [in Albino Rats]. "International Bio-Test

Laboratories, Inc., IBT No. B1982, November 3, 1972.) Altosid was administered via gavage at doses of 0 (corn oil), 500 and 1000 mg/kg to 19-22 pregnant female rats during gestation days 6 through 15. INVALID STUDY. (C. M. Oshita and J. P. Christopher, 5/23/85).

TERATOLOGY, RABBIT

084 001972 Matsumiya, H., Director. "Determination of Teratogenic Potential of Altosid Administered Orally to Rabbit." (Nomura Research Laboratory, Biological Research Department, Japan, Report No. NRI-PL-74-2465, October 1975.) Altosid technical (no purity stated) was administered via gavage at doses of 0 (olive oil), 50, 200, or 2000 mg/kg/day to groups of 10 rabbits (Japanese strain) during gestation days 7-18. Fetuses were examined on day 28. The high dose was selected based on a preliminary test with 3 does/group given a high dose of 4000 mg/kg (not stated if does were pregnant), showing at 13.6% weight decrease (mean first day and final weight only). In the definitive study, there was no mortality but two does aborted at 2000 mg/kg/day. Does at 2000 mg/kg lost weight during days 6 - 18 and gained 40% less days 0 - 28. The initial mean body weight of the high dose group (3.35 $\pm$ 0.65 kg), however, was 22% higher than control mean (2.74 $\pm$ 0.33 kg). Mean number of live fetuses were comparable for pregnant does across groups. The percentage of dead fetuses (implants versus live fetuses) was 6% in controls, 12% at 50 mg/kg, 8% at 200 mg/kg but was 23.1% at 2000 mg/kg. There was no dose-related affect on mean fetal body weights. There were no treatment-related fetal findings. Nominal NOEL = 200 mg/kg (decreased body weight in does, abortions and increased fetal loss at 2000 mg/kg). No adverse effect apparent from the limited data presented. UNACCEPTABLE (major variances including too few animals per group, dose selection poor, limited individual data in the report, no analysis of dosing material, others - see worksheet). Not upgradeable. (J.P. Christopher, 5/23/85; 1-liner by Kishiyama and Gee, 1/31/03).

112 038071 is the same study as 001972.

010 and 027 977545 Ladd, R. and P. S. Smith. "Teratogenic Study with Altosid Technical in Albino Rabbits." (International Bio-Test Laboratories, Inc., IBT No. J1983, November 17, 1972.) Altosid was administered via gavage at doses of 0, 250 and 500 mg/kg to 10-12 pregnant female rabbits during gestation days 6 through 18. No teratogenic effects reported. INVALID STUDY. UNACCEPTABLE (major variances and insufficient information). (C.M. Oshita and J. P. Christopher, 5/23/85).

010 977545 is a duplicate of 027 977545.

TERATOLOGY, MICE

084 001971 Nakasawa, M., A. Nomura, T. Furuhashi, J. Mihori, and E. Ikeya. "Determination of Teratogenic Potential of Altosid Administered Orally to Mice." (Nomura Research Institute, Biological Research Department, Japan, October 1975.) Altosid technical (purity not stated) was administered via gavage to ICR mice at doses of 0 (olive oil), 50, 200, or 600 mg/kg/day during gestation days 7-14 to 30 pregnant female mice per dose. Doses were selected based on a range-finding study to 2400 mg/kg (all died) but no affects were reported at 1200 mg/kg/day. Twenty to 23 pregnant mice were sacrificed on day 18. The remainder (10 - 14) were allowed to litter and pups raised until day 21. Developmental parameters (hair growth, auricle development, and eye opening) were recorded for pups. Weanlings from 5 litters per group (19 - 29 pups) were sacrificed on day 21 and selected organs weighed. The remainder of the pups (19 - 41 per group) were maintained for 7 more weeks and maturation monitored. There were no apparent effects of treatment on any parameter in any group. Nominal NOEL = 600 mg/kg/day. UNACCEPTABLE (insufficient information including no analysis of dosing material, no purity of test article, minimal individual data, no clear toxicity at the high dose so high dose too low).

(C.M. Oshita and J.P. Christopher; 5/24/ 85; edited by Gee, 1/31/03).

112 038070 is the same study as 001971

GENE MUTATION

** 113 047507 Stewart, K. S. and E. S. Riccio "In vitro microbiological mutagenicity assays of Zoecon Corporation's s-methoprene." (SRI International, Project LSC-5854, 9/84) Methoprene, 90%, Batch 542-71, was assayed with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100. Concentrations tested were 0 (DMSO), 10, 50, 100, 500, 1000, 5000 and 10000 ug/plate. There were duplicate plates per concentration in two trials, with and without rat liver activation. There was no increase in revertants in any strain. Positive controls were functional. No adverse effect. ACCEPTABLE. (Remsen, 3/20/86).

127 071067 is the same study as 047507, but lacks summary tables.

111 038069 Hsia, M. T. S., J. A. Adamovics and B. L. Kreamer "Microbial mutagenicity studies of insect growth regulators and other potential insecticidal compounds in Salmonella typhimurium." (Publ. in *Chemosphere* 9: 521 - 529 (1979)). Methoprene (purity not stated) was one of a series of compounds tested with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 with activation from rat liver. Concentrations were 0.2, 2 and 20 μg/plate. Summary data from duplicate plates were reported with no evidence of an increase in reversion rate. UNACCEPTABLE (inadequate number of plates, no trial without activation, no evidence of cytotoxicity at the highest concentration.) Not upgradeable. No worksheet. (Gee, 2/3/03)

CHROMOSOME EFFECTS

010 and 027 977559 Johnston, C. D. "Dominant Lethal Mutagenicity Study with Altosid on Rats." (Woodard Research Corporation, January 1973.) Methoprene (ZR-515, purity not stated) was evaluated for genotoxicity at doses of 0 (saline), 20, 200, or 2000 (undiluted) mg/kg with TEM as the positive control. Five males/group received a single dose (IP) before mating with 2 females/respective group/week for 8 weeks and 5 males/group received 5 consecutive doses (IP) before mating with 2 females/respective group/week for 7 weeks. No evidence of dominant lethal effects reported. UNACCEPTABLE (major variances and insufficient information - see worksheet). Not upgradeable (inadequate number of males) (C. M. Oshita and J. P. Christopher, 5/24/85).

010 977559 is a duplicate of 027 977559.

DNA DAMAGE

** 113 047504, 047505, 047506 Stewart, K. R. and E. S. Riccio "In vitro detection of mitotic crossing-over, gene conversion, and reverse mutation with Zoecon Corporation's compound s-methoprene." (SRI International, Project LSC-5854, 9/84) S-methoprene, 90%, Batch 542-71, was assayed with Saccharomyces cerevisiae, strain D7. Yeast were incubated for 4 hours " rat liver S9 at 0 (DMSO), 0.1, 0.5, 1.0, 2.5 and 5%. There were 5 plates per concentration in two trials. No genetic effect in any assay. No adverse effects. ACCEPTABLE. (Remsen, 3/20/86).

127 071080 same as 113 047504, 047505, 047506. Also includes tabulated data from another study, 113 047507.

OTHER

084 001973 Nakasawa, M. "Rabbit subacute dermal toxicity of Altosid." (Nomura Research Laboratory, Japan, Project no. NRI-PL-74-2465, July, 1975) Altosid technical (purity not stated) was applied to the clipped skin of Japanese rabbits at doses of 0, 0.1, 0.3, 0.9 and 2.7 g/kg/day undiluted (equivalent to 0.1, 0.3, 1.0 and 3.0 ml/kg) for 30 days. The material was applied by a gloved finger tip in a 10 cm circle and not covered. The same site was used for all applications and the sites were not cleaned. Hematology and clinical chemistry (limited parameters for each) and urinalysis were performed. Selected organs were weighed and a larger number preserved for histopathology. There were skin effects (reddening) at 0.3, 0.9 and 2.7 g/kg/day, being most pronounced at the high dose, and "crying" after applications at $\geq$ 0.3 g/kg. There was a tendency for increased liver weight with dose. Local NOEL = 0.1 g/kg/day (clinical signs of skin and related crying). UNACCEPTABLE (method of application, lack of individual data, no description of test article.) Not upgradeable. No worksheet. (Gee, 1/31/03).

030 977524 Jorgenson, T. A. and D. P. Sasmore "Toxicity studies of ZR-515 (Altosid™ Technical): Two-week, range-finding dietary studies in rats and dogs." (SRI, project LSC-1833, 9/6/72) Rats: Weanling Sprague-Dawley rats, 5/sex/group, were fed diets containing 0, 1000, 5000, 10,000, 20,000 or 40,000 ppm of ZR-515 (batch S-1026Z, 68.9%) for two weeks. Rats were fed control diet for 7 days prior to termination. Food consumption was markedly reduced at 20,000 and 40,000 ppm with a related lower body weight. Otherwise, all rats appeared clinically normal. Food intake increased when the two highest dose groups were returned to control diet in week three. Necropsy and gross pathology of the 40,000 ppm group did not indicate any abnormalities (no data). Dogs: Adult male beagles, 3/group, were fed diets containing 0, 1000, 5000, 10000 or 20000 ppm for two weeks. They were returned to control diets for 1 week and terminated at the end of the third week. There was marked reduction in food consumption at 10000 and 20000 ppm, especially in week 1, with a related effect on body weight. Liver weight increased at all treatment levels and was related to the dose. There were no treatment-related lesions in the adrenals, kidneys or spleen. In the liver, swelling and vacuolation were noted but no data presented (Table 11 was missing). Liver sections at 1000 and 5000 ppm appeared normal. UNACCEPTABLE (insufficient information). No worksheet. (Gee, 2/4/03)

030 977534 Olson, W. A. and D. A. Willigan "Three-week subacute inhalation exposure - rats - Altosid™ (technical grade), final report." (Hazleton Laboratories, project no. 777-103, 11/13/72) Two groups of rats, 10/sex/group, were exposed to Altosid (68.9%, density of 0.89 g/cc) for 4 hours/day, 5 days/week, for three consecutive weeks, at nominal concentrations of 2.0 and 20 mg/l. A third group was exposed to air. Exposure was apparently whole body. Clinical studies included hematology, clinical chemistry and urinalysis, with reasonable parameters determined. Only limited tissues were examined microscopically. Text states that rats at 20 mg/l showed nasal discharge (no data). Alkaline phosphatase was slightly elevated at 20 mg/l at termination. No treatment-related pathology was reported. UNACCEPTABLE (insufficient information). No worksheet. (Gee, 2/4/03)

027 977529 Wazeter, F. X. and E. I. Goldenthal "28-day subacute oral study, mouse - Altosid™ Technical." (IRDC, 8/22/73) Altosid™ (86.9%) was fed in the diet to 10 CD-1 mice/sex/group at 0, 500, 1000, 2000, 4000, 8000 or 16,000 ppm for 4 weeks. Male and female mice at 16,000 ppm lost weight and wasted most of their food. At necropsy, white or yellow foci were noted on the liver of 4 females at the high dose, and considered possibly compound-related. No other effects were reported (no data). UNACCEPTABLE (insufficient information). No worksheet. (Gee, 2/4/03)